(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 November 2003 (20.11.2003)

PCT

(10) International Publication Number
WO 03/094905 A1

(51) International Patent Classification[7]: A61K 31/196, 9/00, 31/195

(21) International Application Number: PCT/EP03/04044

(22) International Filing Date: 16 April 2003 (16.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI02A000986 10 May 2002 (10.05.2002) IT

(71) Applicant *(for all designated States except US)*: **AZIENDE CHIMICHE RIUNITE ANGELINI FRANCESO A.C.R.A.F. S.P.A.** [IT/IT]; Viale Amelia, 70, I-00181 Roma (IT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **PINZA, Mario** [IT/IT]; Via per Cesano Boscone, 24, I-20094 Corsico (IT).

(74) Agents: **MARCHI, Massimo** et al.; Marchi & Partners S.r.l., Via Pirelli, 19, I-20124 Milano (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/094905 A1

(54) Title: DICLOFENAC-BASED COMPOSITION FOR THE TOPICAL TREATMENT OF OROPHARYNGEAL CAVITY DISORDERS

(57) Abstract: A composition for the topical treatment of oropharyngeal cavity disorders, comprising an aqueous solution of the salt of diclofenac with tromethamine, in which the amount of the said salt is of from 0.1% to 0.2% (w/w) and the pH is adjusted between 7 and 8.

"Diclofenac-based composition for the topical treatment of oropharyngeal cavity disorders"

* * * * * * * * * * *

The present invention relates to a diclofenac-based composition for the topical treatment of oropharyngeal cavity disorders.

It is known that diclofenac [2-(2,6-dichloroanilino)phenylacetic acid] is a widely-used pharmaceutical product with anti-inflammatory, antipyretic and analgesic properties. It is mainly administered systemically in unmodified form or in the form of a salt thereof with mineral or organic bases.

However, its salts are virtually insoluble in water.

Example 2 of patent US-4 407 824 describes the preparation of the salt of diclofenac with tromethamine [tris(hydroxymethyl)methylamine], but does not specify its solubility in water and does not give an example of any pharmaceutical form containing the abovementioned salt.

The problem of the insolubility in water of diclofenac salts is also acknowledged in EP-A-0 521 393, which proposes to solve the said problem by means of the choline salt. This salt is described as a compound that is surprisingly soluble in water and suitable, inter alia, also for the preparation of mouthwashes.

However, the choline salt has the typical drawbacks of choline, which is well known for its unpleasant odour and taste.

These drawbacks are particularly unfavourable in the case of compositions for the topical treatment of oropharyngeal cavity disorders, for instance mouthwashes and oral sprays, which need to remain in contact with the mucosae for a relatively long period of time in order to exert their therapeutic effect.

Despite the addition of large amounts of ingredients capable of masking its taste [0.5% (w/w) of acesulfame and 35% (w/w) of sorbitol],

compositions for the topical treatment of oropharyngeal cavity disorders based on the salt of diclofenac with choline are relatively unpalatable.

There is therefore still a great need for a diclofenac-based composition of pleasant or at the very least neutral taste, for the topical treatment of oropharyngeal cavity disorders.

Although A. Fini et al. have reported that the solubility in water of the tromethamine salt is considered to be 0.167 g in 100 ml (European J. Pharm. Sci. 4, 231, 1996), the tests conducted by the present inventor have demonstrated that amounts of diclofenac ranging from 0.071 to 0.142 g do not dissolve in 100 ml of water even in the presence of stoichiometric amounts (from 0.029 to 0.058 g, respectively) of tromethamine (Comparative Examples 1 and 2).

Surprisingly, it has now been found that the abovementioned compositions containing from 0.071 to 0.142 g of diclofenac with stoichiometric amounts (from 0.029 to 0.058 g, respectively) of tromethamine in 100 ml of water become clear and remain so for a long time if their pH is brought to 7-8 (Examples 1 and 2).

Also surprisingly, it has been found that the palatability of these solutions is good and that it is also very easy to improve it by means of modest amounts of standard flavouring agents and sweeteners.

One subject of the present invention is thus a composition for the topical treatment of oropharyngeal cavity disorders, characterized in that it comprises an aqueous solution of the salt of diclofenac with tromethamine, in which the amount of the said salt is of from 0.1% to 0.2% (w/w) and the pH is adjusted between 7 and 8.

The preferred concentration of the salt of diclofenac with tromethamine in the composition of the present invention is 0.1% (w/w).

Advantageously, the abovementioned mouthwash comprises other standard ingredients, for instance ethanol, polyhydroxylated alcohols,

complexing agents, preserving agents, humectants, sweeteners, flavouring agents, colouring agents and the like.

Typical examples of these ingredients are:

polyhydroxylated alcohols: glycerol, propylene glycol and polyethylene glycol;

complexing agents: sodium edetate;

preserving agents: methyl p-hydroxybenzoate and propyl p-hydroxybenzoate, sodium benzoate;

humectants: glyceryl polyethylene glycol ricinoleate;

sweeteners: sodium saccharinate, sorbitol, acesulfame and xylitol;

gelling agents: block copolymers of polyethylene glycol and polypropylene glycol such as, for example, Poloxamer™ 407;

flavouring agents: mint flavouring agent, natural tutti frutti flavouring agent and grenadine flavouring agent;

colouring agents: quinoline yellow E 104 and patent blue E 131.

Typical examples of oropharyngeal cavity disorders which benefit from treatment with the composition of the present invention are: gingivitis, glossitis, stomatitis, aphthae, paradentosis, paradentitis, laryngitis, pharyngitis and mucositis caused by radiotherapy and chemotherapy. In addition, the composition of the invention is useful in the treatment of after-effects of dental and/or general surgery.

Preferred dosage forms of the composition of the present invention are mouthwashes and oral sprays.

These dosage forms can be readily prepared according to techniques known to pharmaceutical chemists, and include stages such as mixing, dissolution, sterilization and the like.

The following examples serve to illustrate the invention without, however, limiting it.

Example 1

Mouthwash A

100 g of Mouthwash A contains:

salt of diclofenac with tromethamine*	0.104	g
xylitol	10.000	g
Poloxamer™ 407	0.500	g
sodium benzoate	0.500	g
natural mint flavouring agent	0.500	ml
aqueous solution of E 131 (1 mg/ml)	0.200	ml
pH 7.8 phosphate buffer** qs	100	g
pH	7.6	

* equal to 0.074 g of acidic diclofenac

** one litre of solution in purified water contains: anhydrous dibasic sodium phosphate (5.803 g), anhydrous monobasic potassium phosphate (3.522 g) and 1N sodium hydroxide (18.70 ml).

Example 2

Mouthwash B

100 g of Mouthwash B have the same composition as Mouthwash A except that:

- it also contains natural tutti frutti flavouring agent (0.04 ml) and natural grenadine flavouring agent (0.02 ml), and
- in place of 0.2 ml of aqueous solution of E 131 (1 mg/ml), it contains 0.25 ml of aqueous solution of E 124 (10 mg/ml).

Comparative Example 1

Mouthwash C

A mouthwash was prepared having the same composition as Mouthwash A, except that it contained purified water in place of the pH 7.8 phosphate buffer.

Comparative Example 2

Mouthwash D

A mouthwash was prepared having the same composition as Mouthwash B, except that it contained purified water in place of the pH 7.8 phosphate buffer.

Stability

Mouthwashes A and B were found to be stable.

In contrast, Mouthwashes C and D released over time, especially under cold conditions, a precipitate of diclofenac.

This behaviour was entirely unexpected as regards the mouthwashes containing an amount of salt of diclofenac with tromethamine that is less than the solubility limit reported by Fini et al. (cited above).

CLAIMS

1. Composition for the topical treatment of oropharyngeal cavity disorders, characterized in that it comprises an aqueous solution of the salt of diclofenac with tromethamine, in which the amount of the said salt is of from 0.1% to 0.2% (w/w) and the pH is adjusted between 7 and 8.
2. Composition according to Claim 1, characterized in that it contains 0.10% (w/w) of the salt of diclofenac with tromethamine.
3. Composition according to Claim 1 or 2, characterized in that it further comprises a sweetener selected from the group comprising sodium saccharinate, sorbitol, acesulfame and xylitol.
4. Composition according to any one of the preceding Claims 1 to 3, characterized in that it further comprises a preserving agent selected from the group comprising sodium benzoate, methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.
5. Composition according to any one of the preceding Claims 1 to 4, characterized in that it further comprises a gelling agent consisting of a block copolymer of polyethylene glycol and polypropylene glycol.
6. Composition according to any one of the preceding Claims 1 to 5, characterized in that it further comprises a pharmaceutically acceptable flavouring agent.
7. Composition according to any one of the preceding Claims 1 to 6, characterized in that it further comprises a pharmaceutically acceptable colouring agent.
8. Composition according to any one of the preceding Claims 1 to 7, characterized in that it is used in the treatment of gingivitis, glossitis, stomatitis, aphthae, paradentosis, paradentitis, laryngitis, pharyngitis, mucositis of the oral cavity caused by radiotherapy and chemotherapy, and of after-effects of dental and/or general surgery.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04044

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/196 A61K9/00 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 407 824 A (ECKERT THEODOR) 4 October 1983 (1983-10-04) cited in the application column 1, line 1 - line 25 column 2, line 64 -column 3, line 14 column 10 -column 13; examples 2,9,10,12 claim 1	1-8
A	EP 0 373 103 A (CIBA GEIGY AG) 13 June 1990 (1990-06-13) page 1 -page 2 examples	1-8
A	US 5 972 906 A (FALK RUDOLF EDGAR ET AL) 26 October 1999 (1999-10-26) column 1, line 15 - line 32 column 5, line 9 -column 6, line 15	1-8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 September 2003	02/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Rankin, R

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04044

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 00725 A (FARCON AG) 23 January 1992 (1992-01-23) page 1 page 2, line 13 - line 25 examples claims 1-4	1-8
A	EP 0 521 393 A (FARMAKA SRL) 7 January 1993 (1993-01-07) cited in the application page 1, line 1 - line 15 page 2, line 1 - line 6 examples 2-4	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/04044

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4407824 A	04-10-1983	GB 2093693 A	08-09-1982
		AT 370721 B	25-04-1983
		AT 380166 B	25-04-1986
		AT 136582 A	15-09-1985
		CA 1180008 A1	25-12-1984
		CY 1443 A	10-03-1989
		CY 1444 A	10-03-1989
		FR 2500751 A1	03-09-1982
		FR 2514348 A1	15-04-1983
		GB 2143528 A ,B	13-02-1985
		HK 83888 A	21-10-1988
		HK 83988 A	21-10-1988
		KE 3820 A	09-09-1988
		KE 3821 A	09-09-1988
		LU 83945 A1	13-12-1982
		NL 8100917 A ,B,	16-09-1982
		SE 448088 B	19-01-1987
		SE 8101064 A	18-08-1982
		SE 8203228 A	18-08-1982
		SG 33388 G	30-09-1988
		US 4784808 A	15-11-1988
		US 4551475 A	05-11-1985
		US 4619926 A	28-10-1986
EP 0373103 A	13-06-1990	AT 87476 T	15-04-1993
		AU 624190 B2	04-06-1992
		AU 4434389 A	07-06-1990
		CA 2002472 A1	10-05-1990
		DE 58903964 D1	06-05-1993
		DK 561589 A	11-05-1990
		EP 0373103 A1	13-06-1990
		ES 2054089 T3	01-08-1994
		GR 3007995 T3	31-08-1993
		IE 63482 B1	03-05-1995
		IL 92190 A	23-07-1996
		JP 2178224 A	11-07-1990
		JP 2894744 B2	24-05-1999
		KR 152983 B1	16-11-1998
		NZ 231320 A	25-11-1992
		PT 92228 A ,B	31-05-1990
		ZA 8908554 A	29-08-1990
US 5972906 A	26-10-1999	US 5639738 A	17-06-1997
		US 6103704 A	15-08-2000
		US 5792753 A	11-08-1998
		US 5910489 A	08-06-1999
		WO 9407505 A1	14-04-1994
		WO 9526193 A1	05-10-1995
		WO 9529683 A1	09-11-1995
		WO 9530423 A2	16-11-1995
		WO 9606622 A1	07-03-1996
		WO 9817320 A1	30-04-1998
		EP 0952855 A1	03-11-1999
		US 5834444 A	10-11-1998
		US 5614506 A	25-03-1997
		US 5827834 A	27-10-1998
		US 6022866 A	08-02-2000
		US 5990095 A	23-11-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/04044

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5972906 A		US 6194392 B1	27-02-2001
		US 5852002 A	22-12-1998
		US 5830882 A	03-11-1998
		US 5817642 A	06-10-1998
		US 5811410 A	22-09-1998
		US 6017900 A	25-01-2000
		US 5962433 A	05-10-1999
		US 5977088 A	02-11-1999
		US 5824658 A	20-10-1998
		US 6087344 A	11-07-2000
		US 5817644 A	06-10-1998
		US 6475795 B1	05-11-2002
		US 2002077314 A1	20-06-2002
		US 6114314 A	05-09-2000
		US 5990096 A	23-11-1999
		US 5942498 A	24-08-1999
		US 6218373 B1	17-04-2001
		US 6147059 A	14-11-2000
		US 5914322 A	22-06-1999
		US 6136793 A	24-10-2000
WO 9200725 A	23-01-1992	IT 1243342 B	10-06-1994
		AU 8093591 A	04-02-1992
		CA 2066731 A1	14-01-1992
		DE 491897 T1	14-01-1993
		WO 9200725 A1	23-01-1992
		EP 0491897 A1	01-07-1992
		ES 2034926 T1	16-04-1993
		GR 93300021 T1	28-04-1993
EP 0521393 A	07-01-1993	IT 1250636 B	21-04-1995
		AT 135681 T	15-04-1996
		DE 69209166 D1	25-04-1996
		DE 69209166 T2	25-07-1996
		DK 521393 T3	22-07-1996
		EP 0521393 A2	07-01-1993
		ES 2084878 T3	16-05-1996
		GR 3020190 T3	30-09-1996